# STUDY OF CARBOHYDRATE INTOLERANCE IN PROTRACTED DIARRHOEA

## THESIS

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# C E R T I F I C A T E

This is to certify that the work entitled "THE STUDY OF PREVALENCE OF CARBOHYDRATE INTOLERANCE IN PROTRACTED DIARRHOEA" for the thesis of M.D.(Paediatrics) of Bundelkhand University, has been conducted by Dr. Jagadeesh Ramdas under my direct supervision and guidance in the department of Paediatrics, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department according to University regulations.

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# C E R T I F I C A T E

This is to certify that the work in connection with thesis on "CARBOHYDRATE INTOLERANCE IN PROTRACTED DIARRHOEA", was conducted by Jagadeesh Ramdas in the Department of Biochemistry, under my guidance and supervision. The chromatographic techniques incorporated in this thesis was undertaken by the candidate himself and observations were periodically checked by me.

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# C O N T E N T S



# INTRODUCTION

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Diarrhoeal disease is one of the leading causes of morbidity and mortality among infants and preschool children in developing countries. Majority of the diarrhoeal episodes are acute and self limiting. Protracted diarrhoea is defined as persistence of diarrhoea beyond 2 weeks with at least 4 liquid stools per day, with no weight gain or with weight loss and where conventional line of treatment has failed.

Protracted diarrhoea is associated with deterioration in nutritional status and there is a substantial risk of death.

There are various causes of protracted diarrhoea, viz., Enzyme deficiency, Villous atrophy, persistent infection, inflammatory bowel disease, metabolic disorder etc. Despite the best investigative set-up, etiology of protracted diarrhoea may remain unknown in as many as 30% of infants. Of the known causes, carbohydrate intolerance and milk protein intolerance are the commonest in our country. The hallmark of this disorder in infants is a persistent mucosal injury. Several secondary factors supervene to perpetuate the mucosal

abnormality and lead to vicious cycle of diarrhoea - malabsorption - malnutrition - diarrhoea. Clinically, the severity ranges from critically ill patients requiring sophisticated hospital treatment to those who are moderately ill and recover slowly over weeks or months or promptly with dietary and other therapeutic measures.

Alteration in the digestion and absorption of carbohydrates may lead to carbohydrate intolerance in patients of all age groups. Alteration may occur in the form of primary inborn defect of absorptive ability, involving lactose, sucrose, isomaltose or it could be due to ethnic characteristics of lactose malabsorption which affects a majority of world's population and is given the name of Ontogenetic Lactase Deficiency. Carbohydrate malabsorption may also occur as a result of secondary alteration in the absorptive capacity in a variety of clinical disorders.

Secondary carbohydrate intolerance was first recognised at the beginning of this century in infants with transient lactose intolerance, following gastro-enteritis. A prolonged and severe illness was attributed to the presence of this complication which was alleviated when the offending carbohydrate viz., lactose was eliminated from the diet. It is known that secondary

carbohydrate intolerance is associated with any one of the several diverse systemic and/or intestinal disorders. Secondary carbohydrate intolerance is usually related to a depression of small intestinal oligosaccharidase activity as a result of mucosal damage induced by the primary disease process. The lesion may affect lactase and/or one or all of the mucosal oligosaccharidases. It may also alter the intestinal transport process, and at times even intestinal permeability.

Malabsorption of lactose is a problem of special importance for 2 reasons : 1) the sugar is the major carbohydrate in milk and is poorly absorbed as against all other intestinal disaccharides; 2) the intestinal lactase is the most sensitive of all the intestinal disaccharidases to be affected by intestinal infection. Therefore, lactose malabsorption is one of the most sensitive indicators of mild intestinal insult.

Sugar malabsorption may not only worsen the diarrhoeal symptoms but may also contribute substantially to the perpetuation and promotion of bacterial overgrowth.

Besides, enteritis and diarrhoeal diseases which are the leading causes of carbohydrate intolerance, pathophysiological stress like hypoxia, can also lead to similar condition.

There are various methods for diagnosing this important condition, ranging from simple screening test like demonstration of reducing substance in stool to more sophisticated hydrogen breath test. Among the whole battery of tests are oral lactose loading test, jejunal biopsy and stool chromatography for detecting the offending sugar.

The purpose of this study was to find out the prevalence of carbohydrate intolerance in protracted diarrhoea and to evaluate various diagnostic methods available for the diagnosis of sugar intolerance.

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# REVIEW OF LITERATURE

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Diarrhoea in childhood may be accompanied by secondary alterations in the intestinal mucosa and some deficiencies in the disaccharidase activities. The ingestion of disaccharide during any stage of illness may lead to increased severity of diarrhoea, acidosis and carbohydrate intolerance which improves on elimination of the offending carbohydrate from diet.

Carbohydrate intolerance may be defined as the development of symptoms after the ingestion of carbohydrate either in specific foods or as a specific tolerance test. The symptoms are the result of inadequate digestion and absorption of the sugar. Intolerance may be judged positive when (1) Diarrhoea is induced by feeds, containing the offending sugar, (2) Stool pH is below 6, (3) Stool contains more than 0.5% of reducing agent (Lofshotz, 1910).

The developments that have led to an increased understanding and interest in disorders of disaccharide digestion and in disaccharidase deficiencies have come from laboratories involved in both basic sciences and clinical investigations.

About eighty years ago (1910) Finbelstein and Meyer advocated the feeding of milk with high protein content "EIWESSMILCH" to infant with gastro-intestinal disturbances. These authors believed that whey protein was the substance responsible for the gastro-intestinal disturbances. Later they stated that not only a reduction of whey protein in milk was necessary but also a reduction in milk sugars was required for a complete remission of diarrhoea.

The use and abuse of carbohydrate in infant feeding was discussed by Grulee et al (1912) and Ostheimer et al (1912).

In 1921 Howland described congenital intolerance to carbohydrate and temporary intolerance following diarrhoea. He advocated removal of carbohydrates from the diet of children with prolonged or severe diarrhoea. Renewed interest in diarrhoeal syndromes, associated with maldigestion of specific disaccharides, arose at several pediatric centres. Holzel, Schwartz and Sutcliffe (1959) and Weigers (1962) proposed that a secondary disaccharidase deficiency would be encountered in association with any process which damaged the intestinal cells, such as active or chronic enteritis.

In 1960, Heworth and Ford demonstrated lack of elevation in blood sugar following ingestion of lactose

in patients with gastroenteritis. The fact that intestinal disaccharidases were concentrated in the small intestinal mucosa and more specifically in the microvilli was emphasized by Dahliquist (1960).

Durand et al (1961) used chromatography to demonstrate sugar in stools. He observed that if there was an absolute deficiency of lactase, only then lactose was found in stool while if enzyme deficiency was partial, the respective monohydrates were also found.

In 1962 Giardet described oral lactose tolerance test. Bowce et al (1963) emphasized that the activity of intestinal enzymes was depressed in some acute diarrhoeas. They suggested that high protein diet could, in part, compensate for the decrease in dietetic carbohydrate absorption. They noted that changing from milk to carbohydrate free diet resulted in a dramatic decrease in stool weight, in 69% patients.

In 1965 Gray and Ingelfinger reported that there were four or five maltases and at least one of them hydrolyzed isomaltose and another split sucrose. Authors opined that there could be another sucrase, as well.

There were probably 2 lactases, the major one would reside in the brusb border and the second, a non-specific B-galactoside splitting enzyme that was soluble,

presumably remained concentrated in cellular cytoplasm. Authors demonstrated that the concentration of disaccharidase in the intestinal mucosa was the rate limiting step in disaccharide digestion. They opined that hydrolysis probably occurred at the surface of the microvilli or just within its membrane, since portions of the hydrolysis products were released into the intestinal lumen.

Malcolm et al (1965) suggested that the finding of large amounts of sugar and lactic acid in the stool was due to fermentation of sugar.

Michael et al (1966) reported that lactase activity was lower than maltase or sucrase activity and was the most vulnerable end last to recover. Law and Neole (1966) studied radiographic changes in lactose malabsorption. They found characteristic changes. The small intestine appeared distended by dilute contrast medium, peristalsis was very active, the contrast medium reached the transverse or descending colon within 1 hour while the Haustral pattern was strikingly prominent. Changes of pneumatosis intestinalis may be seen in very severe cases.

The next development that expanded the understanding of disordered disaccharide digestion was the availability of peroral biopsy method that could easily and safely

activities. This was regarded as the most reliable diagnostic means. The technique, difficulties, fallacies and limitations were discussed by Anderson (1966). One such fallacy was that only a tiny fragment of intestinal mucosa would be examined and that could provide misleading information particularly in disaccharidase deficiency secondary to disease of small gut, with patchy lesions.

Enzyme activity is expressed in units per gram of protein. Each unit splits 1 micromole of substance per minute. Burke (1966) gave the normal range of disaccharidase activity in jejunal mucosa in children as follows :

| | Lactase | Sucrase | Isomaltase | Maltase |
|---|---|---|---|---|
| Range | 14 - 132 | 32-228 | 31 - 177 | 83 - 615 |
| Mean | 49 | 95 | 89 | 260 |

Dahlqrist (1966) described a single step ultramicro method for the assay of intestinal disaccharidases which was most suitable for small quantities of mucosa removed by the peroral biopsy method.

Cochet et al (1981) introduced the breath hydrogen test for children with lactose intolerance.

Majority of the carbohydrate malabsorption syndromes are related to alterations in the functional integrity of intestinal mucosa, and its epithelial cells.

Additional intolerance to carbohydrates particularly lactose could be due to other etiologies. Generally 3 classes of intolerance types are recognised (Norbert, 1980) :

(1) Ontogenic Lactose deficiency; also called the physiological deficiency. In this condition the person has either not developed the enzyme or else has lost most of the enzymes function. It could, thus, be seen in premature babies and adults or older children (Cook, 1967). The lactase enzyme develops immediately before birth and around the age of 3 years, it declines to about 10% of its peak values. This decline, increasing with age, takes place in the majority of ethnic groups who consume very little milk. Northern Europeans, Americans, Mongols and the Tusi falani, Nasi Tribes of Africa maintain high levels of lactase throughout adulthood (Delmot, 1968).

At birth jejunal lactase is high in all ethnic groups, irrespective of the status of the enzyme in the adult. In a population where adult hypolactasia prevails, fall in the lactase levels takes place in the first 3-5 years of life. In some cases, an early fall, in the first 6 - 12 months, has been recorded that doubtless accounts for many cases of marasmus (Schrieber et al, 1973). Authors opined that lactase from the breast milk, does not get absorbed and that leads to significant energy loss for the infant.

Zambian population have almost a 100% incidence of adult hypolactasia, and infant diarrhoea during breast feeding is common. After the weaning diarrhoea is reported to stop (King, 1960).

(2) Primary Lactase deficiency - First described by Holzel (1967) and his associates. Primary or congenital lactase deficiency is very rare. Only a few reports of its incidence in the western world are available. Incidence in India is unknown. Most physicians, however, agree that its incidence is less than one in one thousands. Primary deficiency usually becomes manifest very early in life, though it may have a late onset in adults. Patients have a virtual absence of hydrolytic capacity towards lactase, but no other abnormality of intestinal structure or function. The precise biochemical defect responsible for the absence of enzymatic activity has not been characterised. The deficiency may be associated with a complete depletion of enzyme protein or with the presence of an abnormal biologically inactive enzyme molecule. The mode of inheritance of this abnormality has not been clarified. Males are at greater risk (Mcnair, 1972).

(3) Secondary lactase deficiency - Damage to the brush border of the enterocytes and loss of mucosal integrity leads to secondary lactase deficiency. A wide variety of agents are known to cause specific damage to the

lactase enzyme while diverse systemic and gastrointestinal disorders are known to damage villi primarily, leading to reduction of lactase levels. Severe or total villi damage leads to deficiency of all disaccharidases and monosaccharide transport mechanisms (Lindenbaum, 1975).

Lactase is the most superficial of the intestinal oligosaccharidases. Its activity is the rate limiting step for absorption and its concentration is lower than that of other disaccharidases. While decrease in the lactase levels is the main cause of secondary deficiency, other factors such as changes in motility or reduction in absorption surface reduces the exposure time of disaccharides to mucosal enzymes (Ferguson, 1976). Further, the author adds that inflammation or anatomical disturbances could also interfere with enzyme substrate binding, reducing the rate of hydrolytic action to produce a syndrome very similar to secondary deficiency.

Secondary lactase deficiency is thus caused by many factors, the most important of which are mentioned below :

Viral : (1) Rotavirus, (2) Norwalk like agent, Norwalk, (3) Non-specific virus, (4) Measles virus, (5) Hepatitis virus.

Bacteria : Streptococci, shigella, staphylococci, E.coli, Klebsiella, Pseudomonas.

Mycobacteria : Mycobacterium tuberculosis.

Protozoa : Amoeba, giardia (Quinter, 1980).

Candida : has been associated with chronic diarrhoea and subsequent lactase deficiency (Kane, 1976).

1) Rota virus infection is a common case of secondary lactase deficiency and since it occurs in young infants it is a major cause of infant diarrhoea (Flewett, 1976). Viral infection may causes varying degrees of structural changes, ranging from spotty subtotal atrophy to severe flattening of villi and derangement of surface epithelium (Hamilton, 1976).

According to Gall (1978) virus invades the mature cells which have high levels of lactase, consequently immature cells from the crypts migrate towards the tip to take the place of damaged cells. The immature cells tips are lactase deficient, thus leading to intestinal lactase deficiency and diarrhoea.

Systemic viral infections can also cause secondary hypolactasia and malabsorption (Conrad, 1978).

2) Protozoa : The precise cause of malabsorption caused by amoebiasis or giardiasis is not known though a few factors are believed to be involved (Das, 1979). They are : bacterial colonization of the upper small bowel, parasitic

injury to mucosa and tissue invasion, mechanical barriers to absorption and bacterial overgrowth with subsequent bile salt deconjugation.

In patients with giardiasis with secondary lactase intolerance, symptoms may subside immediately after elimination of the parasite (Terruzzi, 1980).

3) Bacteria : Majority of the intestinal bacteria cause damage to the brush border and may produce secondary deficiency. In bacterial diarrhoeas, the malnutrition - gastroenteritis cycle is of great importance since malnutrition predisposes an individual to infection (Chandra, 1982).

4) Malabsorption syndrome : Individuals living in the tropics may show non-specific villous damage due to diet, environmental pathogens, nutritional status etc. Such non-specific villus damage can cause malabsorption of all foods including carbohydrates (Gray, 1982).

5) Hypoxia : Lifshitz et al (1982) have demonstrated, in rats, that hypoxia could cause long lasting depression of lactase activity. Neonatal hypoxia and respiratory distress have also shown to cause lactase deficiency.

6) Surgical resection of small intestine leads to lactase deficiency (Gudmen, 1983).

7) Cow's milk intolerance : Smith et al (1984) have demonstrated that the incidence of lactose intolerance with milk protein intolerance was as high as 92%. They have suggested that allergic reaction in the intestine led to mucosal damage and depletion of lactase.

8) Helminthic infection : Anchylostomiasis, strongyloidiasis are associated with lactase intolerance (Tandon, 1976).

Development of Disaccharidase activity

Maltase, sucrase, and isomaltase in the fetus reache the lower range of normal adult levels by 28-37 weeks of gestation. In both the pre-term and the full term infants their digestion is adequate. In contrast the major digestive enzyme lactase is present at a low level of activity at 28 weeks and then at term the lactase level doubles or triples and reaches adult levels. Theoretically premature infants may be milk intolerant for a few days until their lactase levels reach adequate levels to digest lactose in their milk formula (Stanley, 1950).

Newborn infants nursed on breast milk which contains 7% lactose are said to have several soft acid stools per day, whereas those fed on Cow's milk formulas containing 4% lactase have only one or two alkaline stools. This is presumably due to relative lactose intolerance

A post weaning decrease in lactase activity occurs in most animal species. Experimentally this decrease can be prevented for several additional weeks if lactose is provided as the only source of carbohydrate (Perkin, 1960).

Contrary to the concept that the intestinal disaccharidases are secreted into the succus entericus, digestion of disaccharides occurs intracellularly. This was first shown by Cejori (1962). It appears that all the enzyme activities are highest in the distal part of the villi and epithelial cells are regenerated in the bottom of the crypts and migrate up the sides of the villi and the highest enzyme activity is obtained at the tips of the villi. Galactosidase or lactase activity has been localised in the microsomes by Doell and Kretchmer (1962) while Dehlqrist and Brun (1962) associated their activity with cytoplasmic granules.

Disaccharidase distribution along the small intestine

Enzyme assays in mucosal specimens obtained by peroral intestinal biopsy indicate that sucrase, isomaltase and lactase are less active in the first part than in the remainder of duodenum. In the upper jejunum and the last segments of the ileum, the disaccharidase activity is of the same order and magnitude (Hansen, 1963).

Sugar Transport

Assuming that the disaccharidase splitting enzymes are intracellular, the means by which sugars enter the mucosal cells is obscure. This could be by diffusion, if for instance rapid hydrolysis of the disaccharide within the cell maintained a gradient between it and the intraluminal medium. For glucose and galactose, there also exists an active carrier system (Sinclair, 1963).

A further essential requisite is the presence of sodium ions on the membrane of the mucosal cell. The driving force is regarded, as a form of biological pump, with adenosine triphosphate (ATP) providing the immediate energy source (Burgess, 1964).

Littmann and Hammond (1965) have proposed that sugars enter the intestinal cell by means of a tertiary sugar - sodium carrier complex. This carrier would possess two specific binding sites, one for the substrate and one for sodium ion. The rate of sugar transport seems to be dependent on the difference between intra and extra-cellular sodium concentration and is also mediated by ATP dependent pump.

The probable mechanisms by which diarrhoeal disease leads to malabsorption can be classified as (Twinly, 1966) -

A. Intraluminal events which includes

- Bacterial over growth
- Competition
- Fermentation
- Cross production
- Osmotic effects

B. Cellular events -

- Pharmacotoxic
- Cytotoxic

C. Villous abnormalities.

A. Intraluminal events :

Malabsorption could occur because of events in the lumen which interfere with normal digestive and absorptive process. Due to the bacterial overgrowth the bacterial mass competes with the host for the intake of ingested nutrients (Donaldson, 1967).

The effects of bacterial metabolism of ingested nutrients are important. Bacterial fermentation of sugars occur with the production of gas and short chain fatty acids, both of which are capable of producing gastro-intestinal symptoms and increased water loss. Failure to digest and absorb sugars can also result in an osmotic load in the gastro-intestinal tract and contribute to diarrhoea with secondary effects on vitamin and micro-

nutrient absorption. Finally, the correlation between carbohydrate malabsorption and bacterial counts in the intestine suggest that carbohydrate malabsorption may contribute to, as well as result from bacterial contamination of the gut (Lifshitz, 1972).

It is especially important to look for E.coli strains in the upper gut. E.coli have been isolated in several cases of lactose intolerance (Cufford, 1973).

Clinical lactose intolerance is an uncommon complication of bacterial dysentery indicating that these infection may be more damaging to Colon than to the small intestine (Harry, 1975).

B. Cellular events :

The second major category of pathogenesis relates to the intestinal epithelium and its response to toxins from the lumen of the small intestine. These toxins can be divided into two groups.

i) Pharmacotoxic agents - Studies of xylose and Folic acid malabsorption were done by Lindenbaum (1975) in patients with cholera and other related diarrhoeal diseases. He documented that there is a finite period of malabsorption which may be associated with diarrhoea.

Current evidences however indicate that pharmaco-toxins such as cholera enterotoxin do not affect the

intestinal absorption of sugars and amino acids (Rosenberg, 1978).

ii) Cytotoxic agents - They produce damage with or without invasion of mucosa. Shigella toxin contribute to a cytotoxic effect which interrupts normal intestinal epithelial processes, resulting in defects in intestinal malabsorption. Acute intestinal infection from a variety of cases may be associated with morphological and even villous abnormalities of the intestinal mucosa similar to those associated with more severe chronic forms of malabsorption. There is often a loss of absorbing surface (Ostheimer, 1978).

Drugs - Oral contraceptives are known to depress mucosal lactase though the implication of the observations is not clear, as far as children on breast milk are concerned. Neomycin commonly used for control of diarrhoea has been associated with secondary lactase deficiency. It is believed that this is either a direct effect of the drug or it could be due to antibiotic induced enteropathy (Kistler, 1980).

C. Villous abnormalities :

The major disaccharidases are located in the microvilli of the small intestinal mucosa and if the microvilli are damaged, there is usually a resultant decrease in the activity of all disaccharidases. Lactase

activity which is lower than maltase or sucrase is most vulnerable and last to recover. Decrease in jejunal maximal absorptive capacity may be caused by loss of digestive absorptive cell mass, by permeability disturbances (external or internal), owing to defective hydrolytic and transport mechanisms or as a result of inhibition of brush border function (Rivera, 1980).

The general pattern of rotavirus infection involves virus penetration and infection of the differentiated enterocytes in the villi of small intestine. Rota virus multiplies in the cytoplasm of these cells and causes damage to the digestive and absorptive functions (Marykobestes, 1980).

Sequence of events in the small intestine consist of replacement of the absorptive villous epithelial columnar cells with cuboidal cells and shortening of villi with lymphocyte infiltration. Available evidence suggests that such damaged cells are sloughed into small intestine. Lysis of the infected cells release virus into the intestine. These studies suggest that diarrhoeas caused by rota virus infection is due to malabsorption which also includes impaired carbohydrate absorption. The highly differentiated absorptive villous cells are replaced by immature crypt cells that are not able to compensate for absorption defect (Yates, 1980).

Such changes occur in a cephalo-caudal direction and suggests that much of the diarrhoea is due to loss of absorptive capacity. Histological abnormalities have ranged from mild flattening of the mucosa to complete mucosal atrophy. A decrease in the rate of intestinal cell turnover and decrease in the mitotic index have been noted. Enzyme studies after about 3 weeks of treatment show that the defects in the absorption of monosaccharides and hydrolysis of disaccharides (sucrose, maltose) tend to disappear. However, there is both histochemical and clinical laboratory evidence that the defect in lactose metabolism is the last to get corrected (Leichberg, 1980).

In cases of malnutrition where the gut is previously damaged, gastrointestinal infection or infestation may be a factor in producing an acquired disaccharide intolerance (Valman, 1980).

Normal lactase activity in the jejunum requires more protein than what is necessary for maltase activity. So it will be more easily influenced by the combined effects of malnutrition and gastrointestinal infections. As soon as the inciting cause of mucosal damage subsides, as in acute gastroenteritis, enzyme activity increases. Although lactose tests may become normal, lactase levels remains abnormally low for years. The continued ingestion of lactose may aggravate the acute gastroenteritis

There is no evidence that bacterial fermentation of the disaccharide in the colon has an etiological role in the diarrhoea, through inhibition of absorption (Smith, 1982).

The excess of volatile organic acids especially acetic and lactic acid produced by bacterial fermentation irritate the intestine, which induce peristalsis and excretion of fluid and mucous. Thus, absorption is disturbed with subsequent diarrhoea. Once diarrhoea is present mono-saccharides are also poorly absorbed (Naser, 1983).

Diagnosis of carbohydrate intolerance is suspected at a time when in the history of a diarrhoeal episode there are increasing number of motions and consequent dehydration. The stool are watery, frothy and explosive, accompanied by irritability, abdominal distension and perianal soreness with high stool weight (Lifshitz et al, 1980).

In carbohydrate intolerance (due to lactase deficiency) significant improvement of symptoms occur and a decrease in the stool weight occurs on withdrawal of milk from the diet. Diarrhoea recurs on reintroduction of milk to the diet. Withdrawal of milk from diet decreases the stool weight by 69% (Bowie et al, 1981).

The finding of abnormally large amounts of lactic acid and sugar in the stool while on milk suggests that there is fermentative diarrhoea (Barker, 1981).

Fermentative diarrhoea may be due to malabsorption of mono, di, or polysaccharides. The unabsorbed carbohydrate is subjected to bacterial action which produces organic acid in large quantities as an end product (Weijer, 1982).

Bowie and Brinkman (1981), Ghait et al (1982) and Harry et al (1983) demonstrated the association of disaccharide intolerance and protein calorie malnutrition.

Table showing percentage cases of carbohydrate intolerance in different studies (Ashoka, 1988).

| | Author | Year | Percentage |
|---|---|---|---|
| 1. | Chandra, R.K. | 1968 | 54.0 |
| 2. | Reddy | 1972 | 37.0 |
| 3. | Udani, P.M. | 1976 | 9.32 |
| 4. | Archer | 1977 | 12.0 |
| 5. | Ansari | 1976 | 10.0 |
| 6. | Hirschorn | 1980 | 50.0 |
| 7. | Ghai, O.P. | 1982 | 23.8 |
| 8. | Bhave | 1983 | 37.0 |
| 9. | Clifford | 1983 | 12.0 |
| 10. | Davidson | 1984 | 50.0 |
| 11. | Trounce | 1985 | 10.9 |

Clinical consequences of lactose intolerance

1. Prolongation of diarrhoea : Average duration of rota viral diarrhoea, is 5-7 days. It may get prolonged to 10-14 days due to lactose intolerance, according to Hyams and Krause (1970).

2. Metabolic acidosis : Lactose on fermentation yields lactic acid which is absorbed partially and may stimulate bicarbonate secretion (Rivera et al, 1972).

3. Malnutrition : Carbohydrates form the major source of energy especially in the infant. Since 50% of the calorie requirements are derived from lactose, loss of the sugar to the system leads to caloric defects, even when the diarrhoea is mild.

   Presence of unabsorbed carbohydrate in the lumen also enhances protein and nitrogen loss. Unhydrolysed carbohydrate also interferes with fat malabsorption due to dilution of bile salts (Mcnair, 1972).

4. Bacterial proliferation : The presence of unabsorbed carbohydrates and fermentation products in the small bowel lumen during diarrhoea may facilitate the colonization and proliferation of enteric bacteria in the upper segment of intestine. Such overgrowth of faecal flora in the upper segment of small intestine leads to a state of chronic diarrhoea. Altered

motility, presence of free carbohydrate in the lumen, and other metabolic alterations (luminal pH) are among other factors that influence enteric bacterial dissemination. Bacterial over-population of the upper bowel may generate additional injurious factors such as deconjugated bile salts, hydroxy fatty acids which aggravate intestinal mal-function and worsen diarrhoea (Berr, 1981).

5. Pneumatosis intestinalis may result from carbohydrate intolerance since unabsorbed carbohydrates generate large quantities of gas in the intestinal lumen, which if not expelled may lead to distension of gut with increasing pressure, leading to ischaemia or necrosis of the intestinal mucosa. Thus, providing access for the gas into the tissue spaces and resulting in pneumatosis intestinalis (Vazquez and Amador, 1983).

6. Macromolecular absorption : An increased macromolecular absorption occurs resulting into development of hypersensitivity and allergy to food stuffs. Experimentally it is proved that elevated luminal osmolority leads to enhanced rate of transport of macromolecular traces across the intestinal epithelium (Teichbergs, 1985).

## INVESTIGATIONS IN CARBOHYDRATE INTOLERANCE

1) Stool pH : Stool pH was first suggested by Devidson in 1967. Opinions vary remarkably on the reliability of stool pH in the diagnosis of lactose intolerance.

Measurement of stool pH in lactose intolerance is unreliable, full of fallacies and subject to wide fluctuations according to Martino and Lifshitz (1960). On the other hand Durand (1960) stated that measurement of stool pH was reliable and stool pH was less than 6 in all cases of lactose intolerance.

2) Oral lactose loading test : In 1962 Giardet described oral lactose loading tests, after taking a fasting blood sugar sample. Fifty gm. of lactose dissolved in 400 ml of water was given orally and blood sugar estimated at 15, 30, 60, 90, 120 minutes. If the lactose level was low, blood glucose rise and less than 1.1 m.mol/l.

3) Presence of reducing substances in the stool : Diagnosis of carbohydrate intolerance could be made with Benedict's reagent when reducing substances such as lactose, glucose and galactose are excreted in stools in concentration above 0.25%. The presence of reducing substances could be determined by a change in the colour of diluted fresh stool sample (Joseph, 1976).

In case of sucrose, preliminary hydrolysis using Hcl was done so as to split sucrose into glucose and fructose (Vincent, 1979).

Estimation of stool reducing agents was unreliable technique in the diagnosis of lactose intolerance as opined by Rossi (1990).

4) Rubner's test : This test has been used to detect reducing substances in the stool.

According to Singh et al (1985) incidence of false positive tests was considerably reduced in Rubners method as compared to the conventional benedict's test. To the liquid stool sample lead acetate was added and boiled cooled and then 2 ml of liquid ammonia was added. A pink or red precipitate showed lactose in the stool.

5) Stool chromatography is one of early techniques used in diagnosing cases of carbohydrate intolerance and it continues to be one of the most specific and reliable methods.

Durand et al (1961) used paper chromatography for the first time to identify offending carbohydrate in stool.

Separation and identification of different sugars becomes clear by thin layer chromatography as opined by Joseph (1974).

Thin layer chromatography can pin point the exact offending sugar. It is extremely useful in the

diagnosis of monosaccharide malabsorption where there are rapid changes in the type of food given as observed by Udani (1976).

Bhave et al (1983) observed that stool chromatography was extremely reliable in the diagnosis of lactose intolerance though it was painstaking and time consuming method.

6) Clinitest method : In 1964 Kerry and Anderson developed a new and easy method for the diagnosis of sugar in stool. To 15 ml of stool suspension an indicator tablet was added and a chemical reaction similar to that of urine was seen. This test was not intended to provide conclusive evidence of defective carbohydrate digestion, but indicated that patient could be investigated for sugar malabsorption more intensively.

7) Jejunal biopsy : Quantitative, biochemical assay of disaccharidases in per oral biopsy of intestinal mucosal specimen is regarded as one of the most reliable diagnostic means.

Direct estimation of lactase concentration and the morphology of the biopsy specimen give the idea of the type of hypolactasia. In specific primary hypolactasia the villi are basically normal, together with other disaccharidase concentration (Reddy, 1975).

Small bowel biopsy according to Byrne (1981) is not justified in the diagnosis of carbohydrate intolerance. Since it can be diagnosed better by other non-invasive techniques.

8) Breath hydrogen test : Cochet et al (1981) introduced the breath hydrogen test for children with lactose intolerance. After an overnight fast, lactulose 1 gm/kg as syrup was given orally. Expired breath samples were collected at 0, 60, 90 minutes and analysed for hydrogen concentration. An increase in breath hydrogen, more than 20 parts per million was considered as positive result.

Unabsorbed lactose on fermentation liberates hydrogen and carbondioxide. These gases are finally eliminated through the breath. This technique has the advantage of being non-invasive (Moffei et al, 1982).

According to Bufford et al (1982) breath hydrogen test permits the study of intestinal malabsorption of disaccharidase activity after diarrhoea and may help in deciding the re-introducing of certain carbohydrates into the diet.

Solomon et al (1983) have pointed out that there may be lower hydrogen production in some patients with severe diarrhoea and carbohydrate malabsorption

because the frequency of bowel movements may wash out the colonic bacteria, thus giving false negative results in hydrogen breath test.

9) Radiography in Carbohydrate intolerance :

Law and Neale in 1966 described radiological changes in disaccharidase deficiency.

## TREATMENT

Malcolm et al (1965) advocated the practice of withholding milk in protracted diarrhoea.

Opinion differs as to when milk diet should be restarted. According to Jeffrey et al (1974) it could be started after 10-14 days while Davidson et al (1978) advised a period of atleast 4 weeks.

According to Shub and Walker (1980) oral feeding should be started as early as possible at least partially. The author opines that enteric feedings have a trophic effect on the hypoplastic or damaged intestinal mucosa facilitating early healing and inducing a more rapid return of disaccharidases.

Soyabean preparations were suggested as a milk substitute by Hill & Stuart (1980).

Larcher et al (1980), Bhan et al (1983) and Bhave et al (1983) have emphasized that there may be

intolerance to low lactose formulas due to associated milk protein intolerance and gluten sensitivity. To cope with such situations, authors have deviced some diets prepared from locally available ingredients.

In 1984 Bedline and Boylis suggested that one substrate like glucose could reverse the net secretion and the associated clinical symptoms induced by malabsorption of another substance like lactose.

Larcher et al (1984) have made it clear from numerous animal and human studies, that intraluminal food stuffs, carbohydrates and proteins increase intestinal digestive enzyme and cell proliferation in a dose related way. The inductions are somewhat specific. Sucrose induces sucrase formation. Therefore, a mixed carbohydrate diet was most protective against disaccharidase depletion, during diarrhoea.

Mabel et al (1984) has demonstrated that resumption of milk feeding is associated with prompt improvement in nitrogen balance.

Walker et al (1985) postulated that disaccharidases are continuously being synthesised and degraded in the epithelial cells of the small intestine. Decrease in disaccharidases could be explained by either a decline in the rate of synthesis of new enzyme or an increase in the rate of degradation.

A study conducted by Davidson (1984) revealed that antibiotics do not influence the development of either biochemical or chemical malabsorption of lactose.

According to Sandhu et al (1985) aspirin has been used in the treatment of carbohydrate intolerance associated diarrhoea. Loperamide an opoid has shown greater efficacy in clinical trials in controlling diarrhoea. A recent report suggests that prenylamine, a coronary vasodilator reduces symptoms of lactose intolerance. Prenylamine has been shown to have anti-bacterial effects as it acts by increasing the cell wall permeability.

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# MATERIAL AND METHODS

# MATERIAL AND METHODS

The present study was carried out in the Department of Paediatrics and Department of Biochemistry, M.L.B. Medical College, Jhansi.

## Selection of cases :

The cases included in this study comprised of children presenting with protracted diarrhoea. Cases were picked-up from out-patient and admitted cases of the Department of Paediatrics. Diarrhoea was considered as protracted when it lasted for more than two weeks.

## History and Clinical examination :

In each case a detailed history particularly with regard to diarrhoea, its duration and severity, nature of stool, colour of the motion, presence of mucous or blood was recorded. History of vomiting, abdominal distension, crampy abdominal pain, frothy stools, perianal excoriation, failure to thrive, fever, anorexia was noted. A detailed dietary history regarding the nature of feeds, date when artificial milk was started (including duration of feeds) was noted. Finally the

nutritional history, regarding the average amount of proteins and colories consumed was assessed.

In the physical examination main stress was laid on whether the child had signs of malnutrition. Besides, a general examination of ether systems was done.

Investigations :

Stool examination : Macroscopic examination :- Colour, odour, frothiness and presence of mucous or pus were noted. It was followed by microscopic examination of freshly passed specimen. Stool samples were examined for the presence of ova, parasites and cysts, particularly of giardia and Entamoeba histolytica. Presence of pus cells and red cells were also noted.

Stool culture : In every case stool culture was done at the time of admission.

Stool pH : estimation was done in all samples, immediately after collection. It was done using sensitive narrow range B.D.H. paper. pH estimation was done both at the time of admission and also at the time of discharge.

Stool for reducing substances :

All the samples within 1 hour of collection were tested for reducing substances by Benedict's test.

To 5 ml of Benedict's reagent, 8 drops of liquid stool was added and boiled for about 2-3 mts. and the colour change, especially with precipitate formed, was noted. It ranged from Greenish yellow as 1+, yellow as 2+, orange as 3+ and Brick red as 4+.

In cases where sucrose was suspected as the offending sugar, acid hydrolysis were done. For hydrolysis, stool filtrate was boiled with equal amounts of N/10 Hcl for 30 seconds, prior to testing with Benedict's reagent. Presence of sugar in stool ( 7 5% ) was taken as evidence of sugar intolerance.

Rubner's test : All the samples were subjected to Rubner's test which is yet another test for detecting the presence of reducing substances in the stool.

3-5 ml of liquid stool was taken in a glass tube. To this was added 0.3 - 0.5 g. of lead acetate. The solution was boiled for 2-4 min. and then cooled. Subsequently, 2-3 ml of strong liquid ammonia was added to above solution. It was again boiled for 2-4 min. and then allowed to stand for 5-10 mts. A pink or Brick red precipitate showed sugar in the stool while yellowish or dirty white precipitate showed negative results. If the test was negative, 2-3 ml of strong liquid ammonia solution was again added and the solution

was boiled for 2-4 minutes. After allowing resultant solution to stand for 5-10 minutes, colour of precipitate was again observed. The last procedure was done according to modified Rubner's test.

Stool chromatography : Initially the stool sample was prepared by suspending stool in distilled water, centrifuging and then filtering the supernatant. The filtrate was used directly for chromatography.

Ascending thin layer chromatography method was employed using silica gel as the medium, impregnated on glass slide. The solvent used was a mixture of N. Butanol, glacial acetic acid and distilled water in the ratio of 60 : 30 : 4. The stool sample along with pure standard solution of different sugars like lactose, sucrose, glucose and galactose were placed on the silica gel slide using fine capillary glass tubes. Then, the silica plate was kept in the glass chamber which contained the solvent. By capillary action, the solvent rose on the silica plate and in about 6 - 7 hours, solvent reached the top of plate. The plate was subsequently removed and dried in hot air oven at 110$^{o}$C for about 15 minutes. The chromatograms was then stained using universal iodine dye.

The sugar present in each sample was identified by visual comparison of the sample spot with the spots of the standard sugar samples and a qualitative estimation was done (Stahl, 1969).

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# OBSERVATIONS

## OBSERVATIONS

This study was conducted at the Paediatrics department of M.L.B. Medical College, Jhansi. The study material comprised of children admitted with protracted diarrhoea in the inpatient ward.

The period of study extended for a period of one year from 1st July 1992 to 15th July 1993. During this period 75 children admitted with protracted diarrhoea were studied.

Chromatography was done in the Biochemistry department of M.L.B. Medical College, Jhansi. Cases were taken as positive only when the offending carbohydrate was demonstrated by chromatography.

Table I shows the incidence of carbohydrate intolerance in protracted diarrhoea as revealed by this study.

Table I

Incidence of carbohydrate intolerance in protracted diarrhoea.

| | | |
|---|---|---|
| Total number of cases | : | 75 |
| Cases with sugar intolerance | : | 35 |
| Incidence | : | 46.67% |

Table II

Age incidence of children with carbohydrate intolerance.

| Age of children (months) | No. of cases |
|---|---|
| 1 | 2 |
| 2 | 3 |
| 3 | 2 |
| 4 | 4 |
| 5 | 1 |
| 6 | 1 |
| 7 | 3 |
| 8 | 5 |
| 9 | 6 |
| 10 | 1 |
| 11 | 1 |
| 12 | 1 |
| 15 | 2 |
| 18 | 2 |

52% of the cases were in the age group between 6 to 12 months with peak incidence at 9 months. There was no case more than 18 months of age.

Table III

Sex incidence.

| Sex | No. of cases | Percentage |
|---|---|---|
| Male | 24 | 68.6 |
| Female | 11 | 31.4 |
| Male / Female ratio - 2.2 : 1 | | |

Sex incidence showed a definite male preponderance.

Table IV

Socio-economic status.

| Socio-economic status | No. of cases | Percentage |
|---|---|---|
| Upper income group | 1 | 2.9 |
| Middle income group | 9 | 25.7 |
| Lower income group | 25 | 71.4 |

Most of the cases (71.4%) were seen in the lower socio-economic group.

Table V

Nutritional status according to IAP Classification.

| Nutritional status | No.of cases | Percentage |
|---|---|---|
| Normal | 9 | 25.5 |
| Grade I malnutrition | 11 | 31.4 |
| Grade II malnutrition | 8 | 22.8 |
| Grade III malnutrition | 4 | 11.8 |
| Grade IV malnutrition | 3 | 8.5 |

Nutritional status of the patients showed that majority of the infants were either normal or suffering from early grades of malnutrition.

Table VI

Antibiotics administration.

| | No.of cases | Percentage |
|---|---|---|
| Antibiotics given | 26 | 74.2 |
| Not given | 9 | 25.8 |

Table VI shows the number of children who had received antibiotics prior to admission. In 26 cases (74.2%) the history of administration of antibiotics was present.

Table VII

Dietary History.

| Type of feeds given | No.of cases | Percentage |
|---|---|---|
| Breast milk alone | 4 | 11.4 |
| Breast milk + artificial milk feeds (Cow's, Buffalo's or goat's milk) | 20 | 57.1 |
| Artificial milk feeds alone | 2 | 5.7 |
| Breast milk + proprietary preparations (formula feeds) | 9 | 25.8 |
| Infant formula feeds alone | - | - |

It was seen from the above table that majority of the children (57.1%) received artificial milk feeds alongwith breast feeds. Artificial feeds consisted of Cow's or buffalo milk. No child was kept exclusively on infant formula.

Table VIII

Symptomatology at the time of admission.

| Presenting manifestations | No.of cases | Percentage |
|---|---|---|
| 1. Watery diarrhoea | 30 | 85.7 |
| 2. Semisolid consistency | 5 | 14.3 |
| 3. Fever and vomiting | 21 | 60.0 |
| 4. Fever, vomiting and abdominal distension | 14 | 40.0 |
| 5. Stool frequency : | | |
| a) Less than 5 | - | - |
| b) 5 - 10 | 15 | 42.8 |
| c) More than 10 | 20 | 57.2 |
| 6. Perianal excoriation | 35 | 100.0 |
| 7. Signs of vitamin deficiency | 8 | 22.8 |

The above table shows that 30 (85.7%) cases presented with diarrhoea of watery consistency. All of them also had fever along with vomiting. Abdominal distension was seen in 40% of cases. The stool frequency was more than 10 motions/day in 20 (57.2%) cases, Perianal excoriation was seen in all the cases of protracted diarrhoea with sugar intolerance.

Table IX

Dehydration score (According to W.H.O.)

| Degree of dehydration | No. of cases | Percentage |
|---|---|---|
| Plan A (No dehydration) | 3 | 8.57 |
| Plan B (Some dehydration) | 23 | 65.72 |
| Plan C (Severe dehydration) | 9 | 25.71 |

More than 65% of cases presented with some dehydration and were in Plan B dehydration score according to W.H.O. (1980).

Table X

Associated systemic disease.

| Disease | No. of cases |
|---|---|
| Asthmatic bronchitis | 1 |
| Bronchopneumonia | 2 |
| Viral myocarditis | 1 |
| Encephalitis like picture | 1 |
| Severe anemia | 1 |

Along with protracted diarrhoea, 6 children (17.1%) also had some systemic illness, predominently of respiratory pathology like bronchopneumonia, and asthmatic bronchitis.

Table XI

Duration of diarrhoea.

| Duration | No.of cases | Percentage |
|---|---|---|
| 14 - 28 days | 25 | 71.4 |
| More than 28 days | 10 | 28.6 |

In 71.4% cases having protracted diarrhoea with sugar intolerance mean duration ranged from 14-28 days. Rest had diarrhoea present for longer periods.

Table XII

Stool examination.

| Physical characteristics | No.of cases | Percentage |
|---|---|---|
| 1. Greenish yellow frothy stools | 23 | 65.7 |
| 2. Others | 12 | 34.3 |
| Microscopic examination infestations | | |
| 1. Round worm ova | 3 | |
| 2. Hook worm ova | 4 | |
| 3. Whip worm | - | |
| 4. Giardia | - | |
| Stool culture | | |
| E. coli | 5 | |
| Shigella | 1 | |

In 65.7% of children admitted with protracted diarrhoea and sugar intolerance, stool were greenish yellow and frothy. On microscopic examination, pus cells or fat globules were not detected in any of the cases. Giardiasis also was not detected in the stool.

Stool culture revealed organisms in only 17.1% of cases. The predominant organism isolated was E.coli. One case had shigella isolate in the stools.

Table XIII

pH Range of stool in sugar intolerance cases.

| Stool pH | No. of cases | Percentage |
|---|---|---|
| 6 | 11 | 31.4 |
| 5.5 | 7 | 20.0 |
| 5 | 16 | 45.7 |
| < 5 | 1 | 2.9 |
| Total | 35 | 100.0 |

At the time of admission, 16 (45.7%) cases had a stool pH of 5. In majority of the cases pH ranged between 6 and 5. In only 2.9% of cases was the stool pH less than 5.

Table XIV

Stool reducing substances as detected by Benedict's test.

| Colour and precipitate | Approximate Gm% of sugar | No.of cases | Percentage |
|---|---|---|---|
| Greenish | 0.25 - 0.9 gm% | 25 | 71.4 |
| Yellow | 1.0 - 1.9 gm% | 16 | 45.7 |
| Orange | 2.0 - 2.9 gm% | 2 | 5.7 |
| Brick-red | More than 3.0 gm% | 1 | 2.8 |

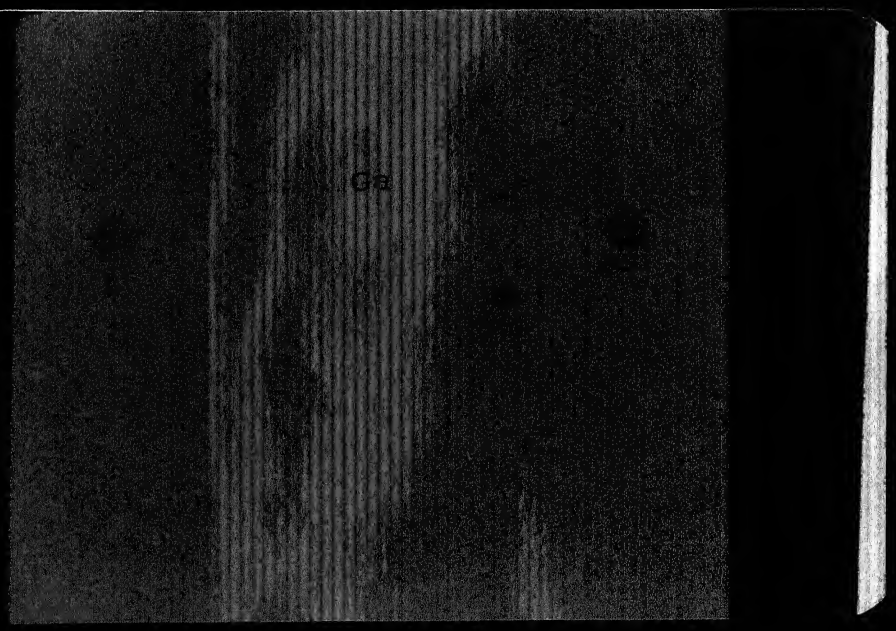
Out of the 75 cases presenting with protracted diarrhoea, 44 cases showed evidence of reducing substances by the Benedict's test. Majority had (0.25 - 0.9 gm%) reducing substance in stool. Only one case had more than 3% sugar in stool.

Table XV

Stool reducing substances as detected by Rubner's test.

| Colour of precipitate | No.of cases | Percentage |
|---|---|---|
| Pink precipitate (Positive) | 37 | 49.3 |
| White precipitate (Negative) | 38 | 50.7 |

Rubner's test was positive in 49.3% of cases.




Photograph showing Sugar Samples on Thin Layer Chromatography

L = Lactose, G = Glucose,

Ga = Galactose, Su = Sucrose,

SS = Stool Sample showing lactose.

Table XVI

Comparative evaluation of Benedict's & Rubner's test.

| Test | True positive | True Negative | False positive | False negative | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Benedict's | 35 | 40 | 9 | 2 | 94.6% | 80.6% |
| Rubner's | 35 | 40 | 2 | 5 | 87.5% | 95.1% |

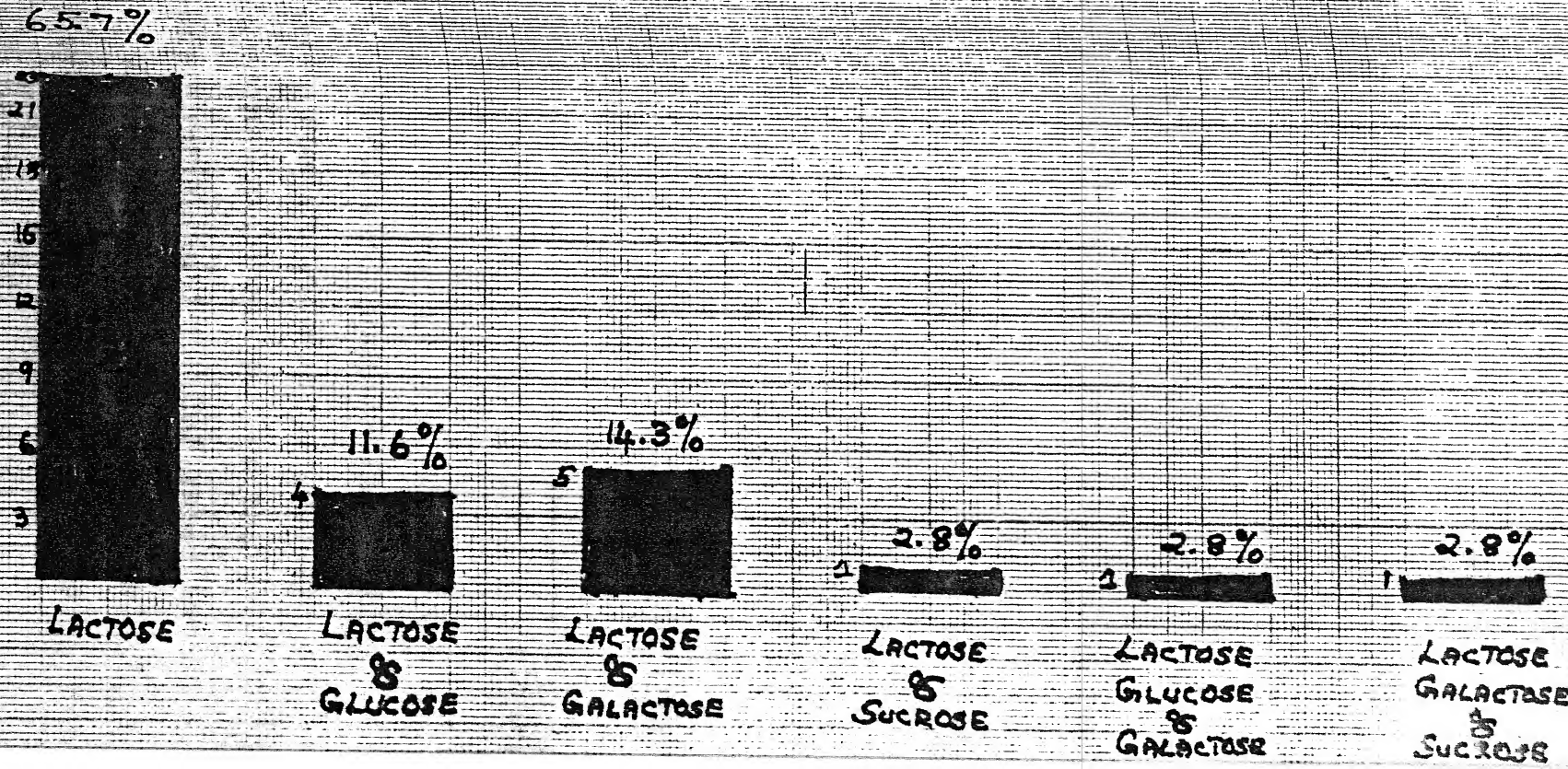
On comparative evaluation there were 9 false positive cases with Benedict's as compared to only 2 cases with Rubner's. But there were 5 false negative cases with Rubner's as compared to only 2 in Benedict's. So in case of sugar intolerance, Benedict's test was more sensitive (94.6%) as compared to Rubner's (87.5%). But it was less specific (80.6%) as compared to Rubner's test (95.1%).

Table XVII

Stool chromatography.

| | No.of cases | Percentage |
|---|---|---|
| 1. Positive | 35 | 46.67 |
| Single sugar | 23 | 65.7 |
| Multiple sugar | 12 | 34.3 |
| | 35 | 100.0 |
| 2. Negative | 40 | 53.33 |

# PATTERN OF SUGAR INTOLERANCE



Out of the total 75 cases, chromatography was positive in 35 (46.6%) cases.

Single sugar was present in 23 (65.7%) out of the 35 cases proved positive for sugar in stool.

Table XVIII

Pattern of sugar intolerance as revealed by chromatography.

| Type of sugar | No.of cases | Percentage |
|---|---|---|
| 1. Lactose | 23 | 65.7 |
| 2. Lactose and Glucose | 4 | 11.6 |
| 3. Lactose, Glucose & Galactose | 1 | 2.8 |
| 4. Lactose and Galactose | 5 | 14.3 |
| 5. Lactose and Sucrose | 1 | 2.8 |
| 6. Lactose, Sucrose and Galactose | 1 | 2.8 |

Of the various sugars lactose was the predominant sugar and was seen alone in chromatography in 65.7% of cases. Multiple sugar was seen in 34.3% of cases. It varied from glucose, galactose and sucrose. Of the multiple sugar intolerance cases, in 3 (28.7%) cases two sugars were detected. While 3 sugars were detected in only 5.6% cases. In no case were four sugars detected in one stool sample.

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# DISCUSSION

## DISCUSSION

Diarrhoea is one of the most important public health problems and a major cause of death among infants in the developing world. In vast majority of cases, diarrhoea in infants is self limited and caused by viral or known bacterial pathogens which are identified by routine stool culture. In some infants, however, inspite of the ordinary supportive measures instituted during the diarrhoeal episode, diarrhoea continues for protracted period. Some of these children are found to have developed intolerance to carbohydrate component(s) of milk at the same time, leading to perpetuation of diarrhoea with its consequences.

According to present study, conducted at the departments of Pediatrics & Biochemistry, M.L.B. Medical College, Jhansi, prevalence of carbohydrate intolerance in protracted diarrhoea was 46.67%. In 1969, Chandra et al used stool pH estimation along with oral lactose feeding test to diagnose lactose intolerance. Thus, he detected lactose intolerance in 54% of cases.

In 1972, Reddy et al used similar methods and detected intolerance in 37% of cases. In 1976, Udani

et al reported a prevalence rate of 9.32%. Larcher et al in 1977, using stool pH estimation along with estimation of reducing agent content of stool, reported a prevalence rate of 12%. In 1982 Ghai et al reported a prevalence rate of 24% for carbohydrate intolerance.

Bhave et al in 1983, employed stool chromatography and reported a figure of 35.7% prevalence rate. In 1984 Davidson et al used the much acclaimed Breath hydrogen test and detected 50% prevalence rate.

These studies only show that the incidence of carbohydrate intolerance is highly variable and depends on the sensitivity of the diagnostic procedures employed as well as the season of study. Perhaps the breath hydrogen estimation test will in future be established as the most sensitive test for early and correct diagnosis of carbohydrate intolerance, but it is very difficult to use in infants.

According to Chandra et al (1969) viral diarrhoeas are more often implicated in the causation of lactose intolerance, and these commonly occur during the winter months. But in this study which was conducted over a period of one year there was uniform distribution of cases with minimal clustering during the summer months.

The present study showed that carbohydrate intolerance was, predominantly, a problem of the latter half of infancy. 52% of the cases in this study were between 6-12 months of age with peak incidence at 9 months. In the study conducted by Ghai et al in 1982 the peak incidence of carbohydrate intolerance was 10.63 months.

That male children are more predisposed to develop carbohydrate intolerance, has been found in several other studies. The male to female ratio as obtained in this study was 2.2 : 1. Trounce et al (1985) found a male to female ratio of 3 : 2 in cases of carbohydrate intolerance. The male preponderance could be a reflection of the traditional Indian family taking more interest in the male sib in all spheres including medical attention. It could also perhaps be explained by the fact that the gene controlling synthesis of immunoglobulin is located in the X chromosome. Since females are homozygous for X chromosome, they have higher levels of immunoglobulin with subsequent higher levels of resistance against invasive micro-organisms.

Out of 75 cases of chronic diarrhoea, 71.4% belonged to the lower socio-economic strata. This is, possibly, because poverty is associated with malnutrition, higher incidence of infection, lack of education and proper hygiene. Parental ignorance and poverty lies at

the root of the problem. 52% of the patients in this study had either normal nutritional status or they fell in grade I malnutrition. Grade II to IV malnutrition was present in the remaining 48% cases.

In 14.88% of the infants above 6 months of age, grade IV malnutrition was observed. The above results emphasize the increased incidence of malnutrition above 6 months of age, probably associated with weaning diarrhoea and the fact that sugar intolerance can occur in all nutritional groups.

Lifshitz et al (1971) found a positive correlation with increasing severity of malnutrition. Udani et al (1976) reported sugar intolerance in all nutritional groups. Kumar et al (1977) found a high incidence of intolerance in well nourished children. Krause et al (1981) showed 50% incidence of sugar intolerance in well nourished babies after acute enteritis. Trounce et al (1985) reported that malnutrition predisposed to lactose malabsorption after acute enteritis.

Protein energy malnutrition is associated with diminished neutrophil function, chemotaxis and phagocytosis, decreased opsonisation, diminished T cell response, diminished secretory IgA levels which tend to perpetuate the infection and further aggravate malnutrition. The lower levels of proteins in protein energy malnutrition

prevent quick regeneration of the destroyed intestinal epithelium.

Antibiotics had been administered to 74 percent of the cases who developed carbohydrate intolerance prior to admission. Kumar et al (1975) reported that 71 percent of infants had received one or more antibiotics. Davidson (1984) reported that 37% had received antibiotics. Perhaps the antibiotics by altering the flora of the intestine, and by destroying the brush border epithelium also had a role to play in the perpetuation of the diarrhoea. Administration of antibiotics indiscriminately during an episode of diarrhoea induces destruction of the intestinal epithelium and subsequent sugar intolerance.

Nearly 12% of children in this study were on breast alone during the diarrhoeal episode, while 57 percent received Cow's or buffalow milk in addition to breast milk. Since the lactose component of breast milk is higher, infants on breast milk are, probably, more prone to develop sugar intolerance. Two infants who were exclusively given artificial feeds had also developed sugar intolerance.

This study also showed that breast feeding did not protect an infant from developing carbohydrate intolerance.

Majority of the children (85%) with sugar intolerance had diarrhoea of watery consistency, while it was semi-solid in consistency in the rest of cases, under study. Other important symptoms were : fever, vomiting and abdominal distension which together were seen in 40% cases. Stool frequency was more than 10/day in 57% cases. Diarrhoea and frequency of stool in sugar intolerance has been attributed to bacterial fermentation of undigested intestinal contents and the osmotic action of large amount of unabsorbed sugar.

Perianal excoriation was found to be a sensitive indicator of the presence of sugar in stool. It was present in all the cases which were positive for sugar, in the present study. Ghai et al (1982) had emphasized this fact. However, the severity of perianal excoriation did not correlate with the extent of sugar malabsorption. Perianal excoriation subsided spontaneously on withdrawal of the offending sugar.

Associated systemic disease, at the time of admission, was seen in 17% of cases. However, the disease showed no correlation to the development of sugar intolerance. The associated diseases were mainly : Asthmatic bronchitis, Bronchopneumonia and severe anemia. Systemic complications would have, probably, contributed to sugar intolerance by necessitating further administration of antibiotics.

Lifshitz et al (1971) emphasized the fact that systemic infection prevented the gut from regenerating destroyed epithelium. Destroyed gut epithelium, besides increasing the sugar intolerance, facilitated rapid entry of pathogenic micro-organisms and their toxins into the blood stream and produced septicemia, endotoxemia, hypersensitivity to various proteins etc.

The macroscopic examination of stool showed that stool were greenish yellow, foul smelling and frothy in 65.7% of cases. Udani et al (1976) had emphasized that stool are large, watery, at times greenish or yellowish in colour, usually had sour smell and often contained mucous in cases of sugar intolerance. Further, authors observed that stool was passed explosively and in the fresh state it was frothy. Ansari et al (1979) have reported that in 76% of cases stool were large, frothy and sour smelling.

Microscopic examination did not revealed any fat globules or pus cells in any of the case (in the present study).

Presence of large numbers of fat globules on stool microscopy in children with sugar intolerance would have suggest concomitant fat malabsorption. Lifshitz et al (1971) reported that steatorrhoea could sometimes be associated with sugar intolerance.

Giardiasis was not seen in any of the cases. It is an important protozoa which may cause disaccharide malabsorption and prolongation of diarrhoea.

Fat malabsorption could be due to deficiency of the enzyme glucosyl ceremidase, which splits glucosyl ceramide present in milk fat vesicles and exists as a complex with lactase, or due to deconjugation of bile salts as a result of colonisation of small intestine by anaerobes.

The pH of the stool was found to be a useful guideline towards the diagnosis of sugar intolerance as observed in the present study. The mean pH of the stool in this study was 5 in 45.7% and 6 in 31.4% cases.

Durand et al (1961) and Davidson (1967) stated that stool pH of less than 6 was characteristic of disaccharide malabsorption and that this was a reliable indicator. Lifshitz (1971) who has done exhaustive work on the problems of sugar intolerance emphasized that stool pH was a reliable indicator. Udani et al (1976) in their study reported that stool pH was below 6 in 61% of cases. It was also noted by the authors that greater the amount of sugar that was detected in the stool, lesser was the pH value.

Ansari et al (1979) in their study reported that pH was less than 6 in 67% of cases of sugar intolerance.

However, oral intake of furazolidine and neomycin, and delay in the performance of test tended to increase the stool pH despite the existence of sugar intolerance. On the other hand infants with metabolic acidosis passed stool with acid pH, that gave false positive indication of sugar intolerance.

McMichael et al (1980) reported that stool pH was highly fluctuant and unreliable in sugar intolerance. Bhave et al (1983) also agreed with the above statement of McMichael. However, consensus of opinion at present is that stool pH could be used as a rough and quick screening test for other diagnostic measures to follow.

Benedict's test for reducing agent in stool showed 0.25 - 0.99 gm% sugar in 71.4% cases. However, presence of reducing agent in stool was not synonymous with sugar intolerance as nine false positive cases were seen which ultimately did not show evidence of sugar on chromatography.

Udani et al (1976) has pointed that that there are many factors which affect the outcome of this test. During an episode of diarrhoea, if the child is on oral rehydration solution some amount of glucose contained in the oral rehydration solution would be excreted in the stool as a result of intestinal hurry. Moreover, if the lactase deficiency of the intestinal epithelium

was only partial, part of the lactose was split into its component monosaccharides that appeared in the stool to give a positive test with Benedict's reagent. In all the cases of present study examination of acid hydrolysed specimen of stool filtrate was done in order to detect sucrose in stool. In this particular study, the sensitivity of Benedict's test was found to be 94.6% while specificity was only 80.6%. Singh et al (1991) in their study pointed out that the specificity of Benedict's test was 78%.

It was found in the present study that Rubner's test was a more specific test as compared to Benedict's. It's specificity in sugar intolerance was 95.1% as compared to 80.6% in Benedict's test. But, it was found to be less sensitive test as compared to Benedict's. Sensitivity was 87.5% as compared to 94.6% in Benedict's test. It was also a simple test requiring two reagents and could be done on the bed side of the patient. Singh et al (1991) reported that modified Rubner's test was more specific test for the detection of sugar in stool.

In this study oral lactose loading test was not done, as many authors have pointed out various disadvantages which limit the use of this diagnostic test. Lactose loading test may result in severe bouts of diarrhoea and requires repeated collection of blood samples which would be unacceptable to many parents.

Udani et al (1976) pointed out that sugar loading test was rarely necessary in routine practice and would be useful only in cases which showed a clinical picture of sugar intolerance and responded to withdrawal of the sugars from the diet, but did not show evidence of sugar in the stool.

Stool chromatography, though a very tedious procedure was found to be an excellent, highly sensitive and reliable indicator of the presence of sugar intolerance. Even mild degrees of sugar intolerance could be detected by this method. In this study lactose alone was present in the stools in 65.7% of cases; 14.3% had lactose in addition to galactose. Lactose was observed in 11.6% cases in addition to glucose, while lactose and sucrose were seen in 2.8% cases. In only 5.6% of the cases was triple sugar intolerance detected. In half of the cases it was lactose, sucrose and galactose intolerance, responsible for the clinical condition.

Stool chromatography has been hailed as a cornerstone procedure for the diagnosis of sugar intolerance by Durand (1961) and Haworth (1963). Moreover, since the development of breath hydrogen test, chromatography has received scant attention.

Bowie et al (1965) studied acquired disaccharide intolerance in malnutrition. Disaccharide intolerance were seen in 52% of the cases which was diagnosed by chromatography. The predominant sugars detected were lactose, glucose and galactose in varying amounts.

Udani et al (1976) in their study detected lactose in stool in 30% of cases and lactose with other sugars in 30% of cases. Sucrose alone was seen in 20% of cases, and glucose alone in the remaining 20% of cases. The intolerance to maltose and fractose was rare, in their study.

If the child was intolerant to lactose alone, it suggested a disturbance in enzymatic hydrolysis of lactose by lactase in the brush border linining the luminal surface of the intestinal epithelium. If the child was intolerant to galactose alone, that suggested complete enzymatic hydrolysis of lactose in the brush border and galactose malabsorption without glucose malabsorption. When lactose and galactose both were detected in the stool, there was, probably, partial enzymatic hydrolysis of lactose resulting in lactose and galactose malabsorption and no glucose malabsorption. When all the three sugars - lactose, galactose and glucose were detected in the stool, there was partial enzymatic hydrolysis of lactose and malabsorption of

all the three sugars. When glucose alone was detected in the stool it was due to the disturbance in active transport mechanism of glucose (Udani et al, 1976).

Joseph et al (1976) reported in their study an incidence of 30 percent sugar intolerance in refractory diarrhoea, diagnosed by Thin Layer Chromatography. Lactose alone was seen in 80% of cases while in the rest it was lactose with sucrose.

Vincent et al (1979) reported an incidence of 59% for sugar intolerance in acute diarrhoea. In 40% of cases it was single sugar intolerance being lactose while in the rest multiple sugar intolerance viz., glucose, sucrose and galactose. Furthermore, authors opined that glucose and fructose could not be differentiated by Thin Layer Chromatography.

Ansari et al (1979) reported in their study that lactose was detected by chromatography in all the cases of sugar intolerance. Besides, there was intolerance to sucrose and galactose in 40% and 20% cases respectively.

Bhave et al (1983) using chromatography reported the incidence of sugar intolerance as 35.7%. They observed single sugar intolerance in all the cases. In 70% it was lactose intolerance while glucose, and sucrose intolerance was seen in 15% cases each

Ashoka et al (1988) reported an incidence of 68% sugar intolerance using chromatography in protracted diarrhoea. Intolerance of lactose with galactose was seen in 3 % of cases. Lactose with glucose was seen in 4% of cases. Triple sugar intolerance with lactose, glucose and galactose was seen in 16% of cases. Only monosaccharides were seen in 17% of cases.

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# SUMMARY AND CONCLUSIONS

# SUMMARY AND CONCLUSIONS

The present study was conducted in the Departments of Paediatrics and Biochemistry, M.L.B. Medical College, Jhansi, for a period of one year from 1st July 1992 to 15th July 1993. The cases included in this study comprised of children presenting with protracted diarrhoea.

Altogether seventy five children presenting with protracted diarrhoea were studied. Aim of this study was to find out the prevalence of carbohydrate intolerance in protracted diarrhoea, to find out the type of sugar intolerance and to evaluate the diagnostic methods available for finding out the sugar intolerance in protracted diarrhoea.

In each case, a detailed history particularly with regard to diarrhoea, its duration and severity and other complaints were noted. A detailed dietary history regarding the nature of feeds, average amount of proteins and calories consumed was recorded.

The diagnostic procedure employed for detecting sugar intolerance was Thin Layer Chromatography. Prior

to that all the screening tests, viz., stool pH, stool reducing substance by Benedict's and Rubner's test were done.

The results obtained are summarized as follows :

1. The prevalence of carbohydrate intolerance in protracted diarrhoea was 46.67%.

2. Carbohydrate intolerance was predominantly a problem of the latter half of infancy with 52% of cases occurring in this age group.

3. There was a definite male preponderance in carbohydrate intolerance (male to female ratio being 2.2 : 1).

4. Sugar intolerance was predominantly a problem effecting the children in the lower socio-economic strata. 71.4% of the cases belonged to this group.

5. More than half (52%) of the patients in this study had either normal nutritional status or they fell in grade I malnutrition. Grade II to IV malnutrition was present in the remaining cases.

6. Antibiotics had been administered to seventy four percent of the cases, prior to admission, who subsequently developed sugar intolerance.

7. More than half (57%) of the children were on Cow's or buffalo milk in addition to breast milk when they developed the problem of sugar intolerance. Another 25.8% cases were on some kind of proprietary preparation in addition to breast milk. Rest of 11.4% cases were exclusively breast fed.

8. Watery diarrhoea was observed in 85% of children suffering from sugar intolerance. Stool frequency was more than 10/day in 57% cases. Perianal excoriation was present in all the cases of sugar intolerance.

9. Nearly 17% of cases had associated systemic diseases, viz., asthmatic bronchitis, bronchopneumonia, severe anemia etc.

10. On macroscopic examination, stool was greenish yellow, foul smelling and/or frothy in 65.7% of cases. No fat globules or pus cells were seen in any of the cases. On microscopic examination, Giardiasis was also not seen in any of the cases. Stool culture revealed organisms predominantly E.coli in 17.1% of cases.

11. Stool pH was 6 or below 6 in all the cases. In 31.4% of cases mean stool ph was 6, while in 45.7% cases it was 5.

12. Benedict's test for reducing agent in stool showed 0.25 - 0.99 gm% sugar in 71.4% cases.

13. It was also found out in the present study that Rubner's test was a more specific test as compared to Benedict's test in finding out sugar intolerance. It's specificity in sugar intolerance was 95.1% as compared to 80.6% in Benedict's test. But Rubner's test was less sensitive, with 87.5% as compared to Benedict's test (94.6%).

14. Stool chromatography was found to be a highly sensitive and reliable indicator of the presence of sugar intolerance. Lactose alone was present in 65.7% of cases. Lactose in addition to galactose was detected in 14.3% cases. In 11.6% cases, lactose was present in addition to glucose, while in 2.8% of cases lactose was seen in addition to sucrose. In only 5.6% of cases triple sugar intolerance was detected.

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# APPENDIX

# WORKING PROFORMA

## STUDY OF CARBOHYDRATE INTOLERANCE IN PROTRACTED DIARRHOEA

Guide : Dr. Ramesh Kumar, MD,DCH,
Professor and Head,
Department of Paediatrics,
M.L.B. Medical College,
Jhansi (U.P.).

Candidate : Dr. Jagadeesh R.

Case No.

OPD/MRD No. _____ Date :

Name of subject : Age/Sex :

Address : D.O.A. :

D.O.D. :

Parental Occupation :

Birth order of child:

PRESENT HISTORY

Diarrhoea : Duration - Acute ( ⩽ 1 week)

- Protracted ( ⩾ 14 days)
- Chronic ( ⩾ 4 weeks)

Severity : Mild (No dehydration)

Moderate (Mild dehydration)

Severe (Moderate to severe dehydration).

Nature of stool : Formed

Semi-solid

Watery

Colour of stool : Yellowish

Greenish yellow

Dark green

Presence of - Mucous

Blood

| | |
|---|---|
| Anorexia | Fever |
| Failure to thrive | Vomiting |
| Abdominal distension | Perianal excoriation |
| Increased flatulence | Number of motions per day |

PAST HISTORY (H/o Similar episodes)

FAMILY HISTORY

1. Hypertension
2. Diabetes
3. Malabsorption

DIETARY HISTORY

| | From | Upto |
|---|---|---|
| a) On breast feeds only | | |
| b) Artificial feeds introduced | | |
| c) Solids introduced | | |

| Nature of artificial milk given | Past | Present |
|---|---|---|
| a) Cow's milk | | |
| b) Goat's milk | | Diluted |
| c) Buffalo's milk | | Undiluted |

Infant formula / Brand / Ratio etc. :

NUTRITIONAL STATUS

Recommended : proteins Calories

Amount consumed :

Malnutrition (IDP Classification) : Grade I - 71 - 80%

Grade II - 61 - 70%

Grade III - 51 - 60%

Grade IV - 50% or below

SOCIO-ECONOMIC STATUS

GENIOLOGICAL HISTORY

ANTIBIOTICS USED

PHYSICAL EXAMINATION

ANTHROPOMETRY

Height : cms. Weight : kg.

Head circumference : cms.

Chest circumference : cms.

Mid-arm circumference : cms.

General Examination :

H.R. : R.R.

Temp.:

Hair : Lack of lusture
Thin & Sparse
Straightness
Dyspigmentation
Flag sign
Easy pluckability

Face : Diffuse depigmentation
Nasolabial dysaesbacea
Moon face

Ant. fontanelle : Flush
Depressed

Eyes : Balot's pspots
Conjunctival xerosis
Corneal xerosis
Keratomalacia
Angular palpepritis
Sunken and dry

Lips : Angular stomatitis
Angular scars
Cheitosis

Teeth : Mottled Enamel

Gums : Spongy, bleeding gums

Glands: Thyroid enlargement
Parotid enlargement
Lymphnode enlargement

Tongue: Atrophic papillae
Scarlet - Oral thrust
Raw tongue

Skin : Follicular hyperkeratosis
Petechiae
Flaky paint dermatitis
Skin turgor

Nails : Kalanychia

Subcutaneous tissue : Odema
Amount of subcutaneous fat

Muscular and Skeletal system :

Muscle wasting
Craniotabes
Frontal and parietal bossing
Epiphyseal enlargement
Beading of ribs
Knock knee or Bow legs

G.I.T. : Hepatomegaly :

Nervous System :

Psychomotor change
Mental confusion
Sensory loss
Motor weakness
Loss of position sense
Loss of vibration sense

Cardiovascular System :

Cardiac enlargement
Tachycardia

## INVESTIGATIONS

Stool : Microscopic examination : Ova
Cysts
Parasites

Culture & sensitivity :

pH - at the time of admission :

at the time of discharge :

Stool reducing substances : Precipitate

| | | |
|---|---|---|
| Greenish yellow | - | 0.25 - 0.99% |
| Yellow | - | 1.00 - 1.99% |
| Orange | - | 2.00 - 2.99% |
| Brick red | - | 3% or above. |

Rubner's Test : Positive / Negative

Stool chromatography :

- Single
- Multiple

Type of sugar identified :

- Glucose
- Galactose
- Lactose
- Maltose
- Sucrose
- Fructose.

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